REMARKS

Applicants have canceled withdrawn claims 35-37 without prejudice. Applicants reserve the right to pursue claims of similar or differing scope in the future.

Applicants note with appreciation that the Examiner has withdrawn claim rejections under 35 U.S.C. § 101 and under 35 U.S.C. § 112, first paragraph (written description).

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Double patenting

Claims 26-34 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-23 of copending Application No. 10/949,720.

In response, Applicants note that claims 1-13 have been canceled, without prejudice, from copending Application No. 10/949,720, rendering the rejection moot. Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejections of Claims under 35 U.S.C. § 103(a)

Claims 26-29, 32-34, and 63-68 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Stephenson et al. (BMC Molecular Biology, 12/21/2001, 2(15):1-9) in view of Queen et al. (US Patent No. 5,693,762).

The Examiner alleges that Stephenson et al disclose that EphB4 is over-expressed in colon cancer (Figure 4, in particular, according to the Examiner) and that therapies targeting EphB4 protein could be used in anticancer treatments (page 2 left column, in particular, according to the Examiner). See Office Action, page 4, lines 14-23.

The Examiner, relying on these teachings, further argues that one of ordinary skill in the art would have been motivated to create radioisotope, fluorescent, enzyme, and enzyme co-factor labeled antibodies (e.g., bispecific, chimeric, human and humanized antibodies) because these

antibodies would function as diagnostic and therapeutic agents that recruit effector molecules (toxins, drugs, prodrugs, cytokines, radionucleotides) or effector cells (cytotoxic T lymphocytes, NK cells, macrophages, granulocytes) to the colon cancer cells expressing EphB4. See Office Action, page 5, lines 1-22.

Applicants respectfully disagree. According to the Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 In View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* (Federal Register Vol. 72, No. 195 at pages 57,526-57,535) (effective October 10, 2007) ("the Guidelines"), a § 103 claim rejection based on a purported teaching, suggestion or motivation to combine prior art references to arrive at the claimed invention must support a conclusion of obviousness by including: (1) a finding that there was some teaching, suggestion or motivation to modify or combine the cited references; (2) a finding that there was a reasonable expectation of success; and (3) whatever additional findings based on the *Graham* factual inquiries may be necessary in view of the specific facts.

As stated by the Supreme Court in *KSR International Co. v. Teleflex Inc.* (550 U.S. __, 82 U.S.P.Q.2d 1385 (2007)) ("*KSR*"), the framework for analyzing obviousness under § 103 remains that which was stated in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) ("*Graham*") and includes the familiar *Graham* factor analysis referred to in the Guidelines above. In particular, the Supreme Court stated *in KSR*:

"Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. **To facilitate review, this analysis should be made explicit.** *See In re Kahn*, 441 F. 3d 977, 988 (CA Fed. 2006) ('**[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness**')" (emphasis added).

First of all, Applicants submit that the Office Action has not satisfied the requirement of establishing a *prima facie* case of obviousness by explicitly stating articulated reasoning for combining the cited references, as is required by case law. Other than the conclusory statements that one of skill in the art would be motivated to create bispecific, single-chain, chimeric, human, and humanized antibodies against EphB4 (see Office Action, pages 5-6), the only reason the Office Action proffered in support of such statements is based on Stephenson's disclosure (page 2, left column) which is copied as below:

"The role of EphB4 and other Eph receptor family members in cancer has not yet been defined, although up-regulation of the expression of several of these has been demonstrated in tumours and cells lines from gastric tissues, prostate, breast, endometrium, and lung [15-23]. Here, we present the results of experiments designed to further investigate the expression of this gene and to clarify its biological relevance to the progression of human colorectal adenocarcinomas. These results suggest that pathways involving Eph-ephrin signalling may be important in the progression of colon cancer and that therapies that target this receptor may find application in anticancer treatment."

Applicants, however, are unable to find where in Stephenson et al. is the alleged teaching that antibodies could be used as diagnostic and therapeutic agents. Stephenson et al. disclose a polyclonal EphB4 antibody (H-200) purely for detecting expression levels of the EphB4 protein. Although Stephenson et al. speculate in the above-mentioned paragraph that "Eph-ephrin signalling may be important in the progression of colon cancer and that therapies that target this receptor may find application in anti-cancer systems," Stephenson et al. **fail** to suggest or teach use of any antibodies as therapies, let alone antibodies against EphB4. Rather, Stephenson et al. are focused on how to reduce EphB4 **expression** for therapeutic purposes. Indeed, Stephenson et al. teach on page 7, left column, under "Conclusions" that:

"*Increased expression* of the EphB4 gene suggests that EphB4 signalling may play an intrinsic role in the development of a tumour phenotype in colon cancer and raises questions concerning this potential role. Further experiments, including targeted disruption of the EphB4 gene

in colon cancer cells and testing the effect of this one the ability of the tumour cells to grow in vitro and vi vivo, may provide useful information for developing strategies for treatment of this disease. Furthermore, the identification of factors that activate the transcription of EphB4 in colon cancer cells may identify signalling mechanisms that are specific to tumour cells. The elucidation of these early events in the signal transduction pathways that lead to development or progression of the tumour cell phenotype may assist in the development of novel detection or prevention strategies" (emphasis added).

Since antibodies (e.g., antibodies against EphB4) would not reduce EphB4 gene expression or have any role in the transcription of EphB4 gene, one of skill in the art would not have been motivated to use antibodies for therapeutic uses based on Stephenson's teachings. Moreover, a skilled artisan would not have been motivated to make even monoclonal antibodies against EphB4 because Stephenson et al. provide no suggestion or reasons to do so.

Although Queen et al. disclose methods for producing humanized immunoglobulins, antibody fragments, bifunctional antibodies, and single chain antibodies, one of skill in the art would not have been motivated to modify the polyclonal antibodies disclosed by Stephenson et al. using the methods taught by Queen et al. Because the skilled artisan would have no reason to believe that the polyclonal antibodies of Stephenson et al. could be of any therapeutic value. Absent any teachings in Stephenson et al. that the EphB4 polyclonal antibody may have any therapeutic value, one of ordinary of skill would not have been motivated to combine Stephenson et al. with Queen et al. to arrive at the claimed invention.

Second, the alleged combination of Stephenson et al. and Queen et al. fails to teach all elements of the claims, such as a monoclonal antibody against EphB4 that promotes apoptosis in a tumor cell. However, the Examiner asserts that "the claiming of the unknown property of inducing apoptosis, which is inherently present in the combined teachings of the prior art, does not make the pending claims patentable. In the absence of evidence to the contrary, the combined teaching of Stephenson et al and Queen would predictably produce the antibodies recited in the pending claims." Office Action, page 6, lines 18-22. The Examiner essentially asserts that the antibody as taught by

the combination of Stephenson et al. and Queen et al. would necessarily possess the claimed characteristics.

Applicant respectfully disagrees because the legal standard for inherent anticipation is **not met** in this case. "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient'" (emphasis added). *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted). "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original). Also see MPEP 2112: "[t]he fact that a certain results or characteristics may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)" (emphasis in original).

This is a strict standard, which requires necessity. Probability, possibility, or even near certainty (*e.g.*, "almost always") would not satisfy the legal standard.. *See In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

Therefore, if all antibody against EphB4 would possess the technical feature of promoting apoptosis in a tumor cell (as the Examiner assumed), then it might be true that monoclonal antibodies against EphB4 (including bispecific, single-chain, chimeric, human, and humanized antibodies) necessarily promote apoptosis in a tumor cell.

However, the Examiner has not provided any scientific basis to support such assumption. To the contrary, it is well known in the art that antibodies are unpredictable in nature. Indeed, the Board of Appeal noted that: "[h]ybridoma technology is an empirical art in which the routineer is unable to foresee **what particular antibodies** will be produced and which specific surface antigens will be recognized by them (emphasis added)." Ex parte Old, 299 U.S.P.Q. 196, 200 (PTO Bd. App. 1985).

One of skill in the art would know that not all antibodies against EphB4 is capable of promoting apoptosis in a tumor cell. For example, the specification provides Example 10 (pages 102-104) and in particular, Figure 59 to assess the ability of EphB4 antibodies to promote apoptosis in a tumor cell. Of the antibodies which were tested, antibody #91 showed no change in apoptosis (see Figure 59; and page 104, line 4). This data further substantiates the conclusion that hybridoma technology is an empirical art and a skilled artisan is unable to foresee **what particular antibodies** will be produced.

Accordingly, it is logically unsound for the Examiner to assume that monoclonal antibodies against EphB4 (including bispecific, single-chain, chimeric, human, and humanized antibodies) necessarily promote apoptosis in a tumor cell. Therefore, Stephenson et al. and Queen et al., singly or in combination, fail to inherently teach all elements of the claims.

In sum, Applicants submit that all of the pending claims are non-obvious over Stephenson et al. in view of Queen et al. Applicants respectfully request reconsideration and withdrawal of the rejection of the pending claims under 35 USC § 103.

Rejections of Claims under 35 U.S.C. § 103(a)

Claims 26-29, 32-34, and 63-68 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Inada et al. (Blood, 1997, 89(8):2757-2765), in view of Stephenson et al., and in further view of Queen et al. (US Patent No. 5,693,762). Applicants respectfully traverse these rejections.

Applicants reiterate the arguments already made above for rebutting the obviousness rejection over Stephenson et al. Like Stephenson et al., Inada et al. do not suggest or teach any therapeutic use or potential of the EphB4 antibody. Inada et al. merely use antibodies to EphB4 to isolate arythroid progenitor cells. No diagnostic or therapeutic benefits of these antibodies have been disclosed. The other cited references (e.g., Queen et al. and Stephenson et al.) fail to cure the deficiencies of Inada et al. Absent any teachings in Inada et al. that the EphB4 antibody may have any therapeutic value, one of ordinary of skill would not have been motivated to modify Inada's

antibodies to make bispecific, single-chain, chimeric, human, and humanized antibodies against EphB4 as claimed in the present invention.

Further, like Stephenson et al, Inada et al. do not teach, expressly or inherently, an isolated EphB4 antibody which promotes apoptosis in a tumor cell. Therefore, the proposed combination of the cited references fail to teach each and every limitation of the claimed invention.

In sum, Applicants submit that all of the pending claims are non-obvious over Inada et al. in view of Stephenson et al., and in further view of Queen et al. Applicants respectfully request reconsideration and withdrawal of the rejection of the pending claims under 35 USC § 103.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000. If an additional fee is due, the Commissioner is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 18-1945, under Order No. **VASG-P01-002**. Please direct any questions arising from this submission to the undersigned at (617) 951-7000.

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Respectfully submitted,

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